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Via Federal Express

Document Processing Center (Mail Code 7407M)
Room 6428
Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency, ICC Building
1201 Constitution Ave., NW
Washington, DC 20460

COMPANY SANITIZED

Dear 8(e) Coordinator:

8EHQ-02-15093
Anthranilamide

This letter is to inform you of the results of a recently completed one-generation reproduction study in rats with the above referenced test substance.

A one-generation reproduction study was conducted in which the test material was administered in the feed to groups of male and female rats (10/group), the P_1 generation, at dietary concentrations of 0, 300, 1500 or 5000 ppm. Rats were fed for 2 weeks prior to cohabitation (premating period), during the cohabitation period (up to 2 weeks), and during gestation and lactation. Cage side observation for mortality and moribundity were performed daily. Clinical signs were recorded weekly. Body weights were recorded weekly during premating and cohabitation and on days 0, 7, 14, 21 of gestation and lactation for P_1 generation rats. Body weights were recorded weekly for F_1 generation rats beginning at weaning on postnatal day (PND) 21. Food consumption was recorded with body weights, except for the P_1 cohabitation and lactation periods, when food consumption was not determined. A functional observation battery (FOB) and motor activity (MA) were evaluated in P_1 male and female rats at the end of the 2-week premating period. F_1 pups were counted by sex and individually weighed at birth, and on PND 4, 7, 14, and 21. F_1 pups were culled to 8 per litter on PND 4 and unselected pups discarded without further evaluation. On PND 21, 1 pup/sex/litter was randomly selected and retained to comprise the F_1 generation; unselected weanling pups (3/sex/litter) underwent a gross pathological examination. The F_1 generation rats were not exposed after PND 21. At necropsy (P_1 females on lactation day 21; P_1 males after siring litters, F_1 generation at PND 60), testes, epididymides, prostate, seminal vesicles, uterus, ovaries, thyroid, and liver, were weighed and retained for possible histopathological examination. The number of uterine implantation sites was recorded in P_1 females.

At the high dose level, three females were found dead on the second day of the study. They were replaced with three extra females; one of these females was found dead the next morning. This animal was replaced with an extra female, which survived the first day of diet administration and thereafter. No clinical signs of toxicity were observed in the P_1 or F_1 generation rats, or in the F_1 litters during lactation. In P_1 females fed 5000 ppm, body weight gain and food consumption on days 7-14 of gestation were 79% and 90% of control, respectively. Overall gestation body weight gain was 89% of control in P_1 females at 5000ppm.

There was no effect on FOB parameters or MA in P_1 rats. There were no compound-related effects on the following reproduction parameters: mating and fertility indices, gestation length, number of uterine implantation sites, implantation efficiency, number of pups born, born alive, and alive on PND 4, 7, 14, and 21. Litter sex ratio, gestation index, percent pups born alive, lactation index, and litter survival were unaffected at any dose level. A statistically significant reduction in 0-4 Day viability of F_1 pups was observed at the mid and high dose levels (97-98% vs. 100% in control group). F_1 pup weights were significantly reduced on PND 0-4 and 0-7 at the mid and high dose, respectively (91-94% of control). In the F_1 generation, body weight gain was significantly reduced at the high dose level on PND 21-28 in males (88% of control) and PND 28-42 in females (82-84% of control). Food consumption was significantly reduced in F_1 males at the mid and high dose level (86-90% of control) on PND 21-35. The mean age at preputial separation and vaginal opening in F_1 generation rats were unaffected at any dose level.

Liver weight was significantly increased in P_1 male and female rats at the mid and high dose level, whereas thyroid weight was increased at the high dose level in P_1 male rats only. Thyroid weight was decreased in F_1 females, but not in F_1 males, at the mid and high dose level. Other organ weights were unaffected in P_1 and F_1 generation rats. There were no other gross pathological findings in the study.

The liver and thyroid gland were examined microscopically in P_1 and F_1 generation rats. Hepatocellular hypertrophy, characterized by cells with an enlarged and homogeneously eosinophilic cytoplasm, was observed at all dose levels in P_1 male and female rats. This observation was not present in the F_1 generation. Hepatocellular hypertrophy was considered an adaptive physiologic response to exposure to a xenobiotic and not biologically adverse. Follicular thyroid hypertrophy and/or colloid depletion were observed at the mid and high dose level in P_1 male and female rats. Follicular hypertrophy was characterized by follicles lined with columnar, rather than cuboidal epithelium. Colloid depletion was diagnosed when the usually eosinophilic follicular colloid was markedly pale and/or absent. Follicular hypertrophy was observed in 1 and 2 F_1 males at the mid and high dose level, respectively.

Under these experimental conditions, the findings described above appear to be reportable, based upon guidance given in the EPA TSCA Section 8(e) Reporting Guide (1991).

Sincerely,